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United States Patent [19]

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Ruddy et al.

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- [54] **COMPOSITIONS OF IODOPHENOXY ALKYLENE ETHERS AND PHARMACEUTICALLY ACCEPTABLE CLAYS FOR VISUALIZATION OF THE GASTROINTESTINAL TRACT**
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- [73] Assignee: **Sterling Winthrop Inc.**, New York, N.Y.
- [*] Notice: The portion of the term of this patent subsequent to Sep. 20, 2011, has been disclaimed.

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FOREIGN PATENT DOCUMENTS

[21] Appl. No.: **237,502**

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[22] Filed: **May 3, 1994**

Related U.S. Application Data

- [63] Continuation-in-part of Ser. No. 222,787, Apr. 4, 1994, which is a continuation-in-part of Ser. No. 29,485, Mar. 11, 1993, Pat. No. 5,348,727.
- [51] Int. Cl.⁶ **A61K 49/04**
- [52] U.S. Cl. **424/9.45**; 514/520; 514/522; 514/570; 514/716; 514/718; 514/720
- [58] Field of Search 424/5, 9.45; 558/414, 558/423; 562/470; 568/649; 514/520, 522, 570, 716, 718, 720

Primary Examiner—Gary E. Hollinden
Attorney, Agent, or Firm—Fish & Richardson

[57] ABSTRACT

Disclosed are x-ray contrast compositions for oral or retrograde examination of the gastrointestinal tract comprising iodophenoxy alkylene ethers and pharmaceutically acceptable clays in a pharmaceutically acceptable carrier; and methods for their use in diagnostic radiology of the gastrointestinal tract.

[56] References Cited

U.S. PATENT DOCUMENTS

2,348,231 5/1944 Strain et al. 260/476

22 Claims, No Drawings

**COMPOSITIONS OF IODOPHENOXY
ALKYLENE ETHERS AND
PHARMACEUTICALLY ACCEPTABLE
CLAYS FOR VISUALIZATION OF THE
GASTROINTESTINAL TRACT**

This application is a continuation-in-part of application Ser. No. 08/222,787, filed on Apr. 4, 1994, which in turn is a continuation-in-part of application Ser. No. 08/029,485, filed on Mar. 11, 1993, now U.S. Pat. No. 5,348,727.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to aqueous x-ray contrast compositions containing an iodophenoxy alkylene ether as the contrast agent and a pharmaceutically acceptable clay for oral or retrograde administration to a mammal, and methods for their use in diagnostic radiology of the gastrointestinal tract.

2. Reported Developments

Roentgenographic examination utilizing x-rays and computed tomography (hereinafter CT) scans of fractures and other conditions associated with the skeletal system is routinely practiced without the use of contrast agents. X-ray visualization of organs containing soft tissue, such as the gastrointestinal (hereinafter GI) tract, requires the use of contrast agents which attenuate x-ray radiation. D. P. Swanson, et al in "Pharmaceuticals In Medical Imaging", 1990, MacMillan Publishing Company, provides an excellent background in medical imaging utilizing contrast agents and compositions therewith.

Roentgenographic examination of the GI tract is indicated for conditions of digestive disorders, changes in bowel habit, abdominal pain, GI bleeding and the like. Prior to radiological examination, administration of a radiopaque contrast medium is necessary to permit adequate delineation of the respective lumen or mucosal surface from surrounding soft tissues. Accordingly, a contrast medium is administered orally to visualize the mouth, pharynx, esophagus, stomach, duodenum and proximal small intestine. The contrast medium is administered rectally for examination of the distal small intestine and the colon.

The most widely used contrast agent for the visualization of the GI tract is barium sulfate administered as a suspension orally or rectally as an enema. (See, for example, U.S. Pat. Nos.: 2,659,690; 2,680,089; 3,216,900; 3,235,462; 4,038,379 and 4,120,946) Notwithstanding its relatively good contrast characteristics, negligible absorption from the GI tract following oral or rectal administration and speedy excretion from the body, barium sulfate has certain disadvantages. In the presence of intestinal fluids it lacks homogeneity and poorly adheres to mucus membranes which can result in poor x-ray images. In the colon, when administered as an enema, it flocculates and forms irregular clumps with fecal matter.

Iodinated organic compounds have also been used as GI contrast agents since the iodine atom is an effective x-ray absorber. They have the most versatility and are utilized in the widest variety of procedures. They are very absorptive of x-rays with which the iodine interacts and produce a so-called photoelectric effect which is a large magnification in contrast caused by the photons stopped in the iodine-containing medium. The magnification of contrast exceeds the level that would be expected from relative changes in density. Because of this magnification, relatively low con-

centrations of the contrast agent can be utilized. (For iodinated agents see, for example, U.S. Pat. Nos.: 2,786,055; 3,795,698; 2,820,814; 3,360,436; 3,574,718, 3,733,397; 4,735,795 and 5,047,228.)

The desiderata for an ideal GI contrast agent includes: good toxicological profile; the ability to fill the entire bowel/lumen and evenly coat the gut mucosa so that the presence of the bowel is detectable when the lumen is not distended; and nonirritation to the intestinal mucosa; and passage through the GI tract without producing artifacts or stimulating vigorous intestinal peristalsis.

These requirements were addressed by many investigators and their efforts resulted in great improvements over the years. The requirement of evenly coating the gut mucosa with a contrast agent to effectively cover the walls of the intestines proved to be rather difficult. Without meeting these requirements it is impossible to obtain x-ray pictures of high precision. To that end, the use of certain polymer additives were proposed as illustrated hereunder.

U.S. Pat. No. 4,069,306 discloses an x-ray contrast preparation which is said to adhere to the walls of body cavities. The preparation comprises a finely divided water-insoluble inorganic x-ray contrast agent and minute particles of a hydrophilic polymer which is insoluble in water but is water-swallowable. The body cavity is supplied with such preparation suspended in water. The x-ray contrast agent is present in admixture with and/or enclosed in and/or adhered to said minute polymer particles.

U.S. Pat. No. 4,120,946 discloses a pharmaceutical composition for barium opacification of the digestive tract, comprising colloidal barium sulfate and a polyacrylamide in an aqueous vehicle. The polyacrylamide forms a viscous solution at low concentration which makes it possible to maintain the barium sulfate in suspension and at the same time permit good adherence of the preparation to the walls of the organ which it is desired to x-ray.

U.S. Pat. No. 5,019,370 discloses a biodegradable radiographic contrast medium comprising biodegradable polymeric spheres which carry a radiographically opaque element, such as iodine, bromine, samarium and erbium. The contrast medium is provided either in a dry or liquid state and may be administered intravenously, orally and intrarterially.

While these polymeric materials greatly enhance attachment of the contrast agent used therewith to the walls of organs for better visualization thereof, there is still a need for an improved x-ray imaging medium that uniformly coats the soft tissues subjected to diagnostic x-ray examination.

We have now discovered that the use of certain natural clays in combination with an x-ray producing agent enhance the uniformity of coating on the gastrointestinal tract and the quality of x-ray images. In addition, these clays mask the unpleasant odor and taste of the x-ray contrast formulations as well as enhance the physical stability thereof.

SUMMARY OF THE INVENTION

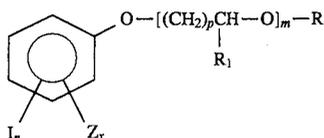
It is the object of the present invention to provide compositions for coating the gastrointestinal tract of mammals to form an effective radiopaque coating thereon by which diagnostic examination of the GI tract may be accomplished.

The object of the present invention is achieved by a composition comprising: an iodophenoxy alkylene ether as an x-ray contrast agent and a pharmaceutically acceptable clay in an aqueous pharmaceutically acceptable vehicle.

3

In accordance with the invention there is further provided a method for x-ray diagnostic imaging of the GI tract which comprises orally or rectally administering to the patient an effective contrast producing amount of the above-described x-ray contrast composition.

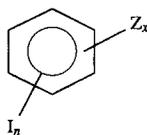
The composition for radiological examination of the GI tract comprises a compound of the formula or a pharmaceutically acceptable salt thereof:



wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, alkoxy-carbonyl, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl,



or halo-lower-alkyl; each of which may be optionally substituted with halo, fluoro-lower-(CR₁R₂)_p-(CR₃=CR₄)_mQ, or (CR₁R₂)_p-C≡C-Q;

R₁, R₂, R₃ and R₄ are independently H or lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-4;

m is 1-15;

p is 1-20; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl.

As used herein, the term halogen (or halo) means fluorine, chlorine, bromine or iodine.

As used herein, the term cycloalkyl means carbocyclic rings having from three to eight ring carbon atoms including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclooctyl which may be substituted on any ring carbon atom thereof by one or more lower-alkyl groups, lower-alkoxy groups or halogens.

As used herein the terms lower-alkyl and lower-alkoxy mean monovalent aliphatic radicals, including branched chain radicals, of from one to ten carbon atoms. Thus, the lower-alkyl moiety of such groups include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, n-hexyl, 1-methylpentyl, 3-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, 1,1,3,3-tetramethylpentyl, 1,1-dimethyloctyl and the like.

As used herein, the term lower-alkenyl and lower-alkynyl means monovalent, unsaturated radicals including branched chain radicals of from three to ten carbon atoms and thus include 1-ethenyl, 1-(2-propenyl), 1-(2-butenyl), 1-(1-methyl-2-propenyl), 1-(4-methyl-2-pentenyl), 4,4,6-trimethyl-2-heptenyl, 1-ethynyl, 1-(2-propynyl), 1-(2-butylnyl), 1-(1-methyl-2-propynyl), 1-(4-methyl-2-pentynyl) and the like. 2-heptenyl, 1-ethynyl, 1-(2-propynyl), 1-(2-butylnyl), 1-(1-methyl-2-propynyl), 1-(4-methyl-2-pentynyl) and the like.

4

As used herein, the term alkylene means divalent saturated radicals, including branched chain radicals of from two to ten carbon atoms having their free valences on different carbon atoms and thus includes 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1-methyl-1,2-ethylene, 1,8-octylene and the like.

As used herein, the term aryl means an aromatic hydrocarbon radical having six to ten carbon atoms. The preferred aryl groups are phenyl, substituted phenyl and naphthyl substituted by from one to three, the same or different members of the group consisting of lower-alkyl, halogen, hydroxy-lower-alkyl, alkoxy-lower-alkyl and hydroxy.

The x-ray contrast compound can comprise one, two, three or more iodine atoms per molecule; preferred species contain at least two, and more preferably, at least three iodine atoms per molecule.

The solid x-ray contrast agents in particulate forms useful in the practice of the present invention can be prepared by techniques known in the art. The solid agents are comminuted to the desired size using conventional milling methods, such as airjet or fragmentation milling. We have found that an effective average particle size of less than about 100μ provides for good distribution and coating in the GI tract. As used herein, particle size refers to a number average particle size as measured by conventional techniques, such as sedimentation field flow fractionation and disk centrifugation. An effective average particle size of less than about 100μ means that at least about 90% of the particles have a weight average particle size of less than about 100μ as measured by art recognized techniques.

The compositions may be in the form of dispersions, suspensions, when the x-ray contrast agent is a solid, or emulsions, when the x-ray contrast agent is an oil; we prefer to use emulsions as the preferred embodiment.

The natural clays incorporated in the compositions of the present invention are selected from the group consisting of montmorillonite, beidellite, nontronite, hectorite and saponite.

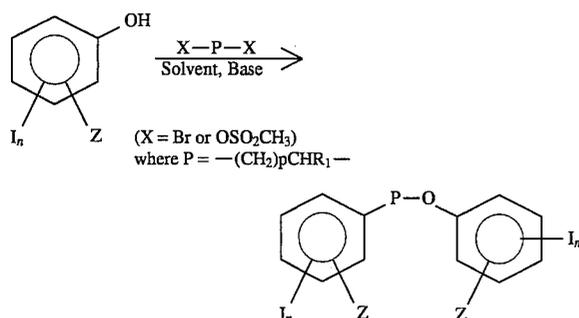
The contrast agent and the pharmaceutically acceptable clay are formulated for administration using physiologically acceptable carriers or excipients in a manner within the skill of the art. The contrast agent and the pharmaceutically acceptable clay with the addition of pharmaceutically acceptable aids (such as surfactants and emulsifiers) and excipients are suspended in an aqueous medium resulting in a dispersion, suspension or emulsion.

A method for diagnostic imaging of the GI tract for use in medical procedures in accordance with this invention comprises orally or rectally administering to the mammalian patient in need of an x-ray examination, an effective contrast producing amount of a composition of the present invention. After administration at least a portion of the GI tract containing the administered composition is exposed to x-rays to produce an x-ray image pattern corresponding to the presence of the contrast agent, then the x-ray image is visualized and interpreted using techniques known in the art.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of the present invention can be made according to the schematic procedure shown or other methods using commercially available starting materials, intermediates and reagents. Starting materials, reagents and solvents can be obtained from chemical suppliers such as Aldrich, Baker and Eastman Chemical Companies, or they may be prepared by techniques known in the art.

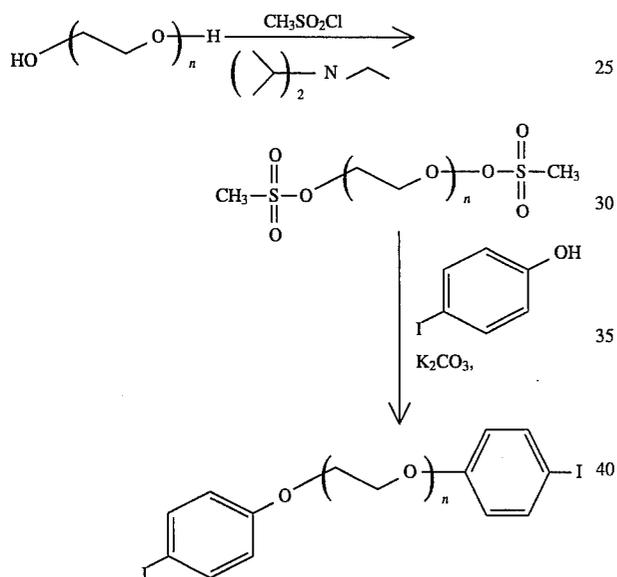
Scheme 1



The following examples will further illustrate the compounds used in the present invention.

EXAMPLE 1

Bis-(4-iodophenyl) ether of polyethylene-glycol-400



A. Preparation of bis-mesylate of polyethylene-glycol-400

(PEG-400)

To a solution of PEG-400 (40.0 g, 100 mmol) in dry CH₂Cl₂ (200 ml) at 4° C. was added diisopropylethylamine (43.5 ml, 250 mmol). After 10 min, methanesulfonyl chloride (17.0 ml, 220 mmol) was added as a solution in CH₂Cl₂ (40 ml) over a period of 0.4 hr. After 2.5 hrs, the reaction was diluted to 500 ml with cold CH₂Cl₂ and poured over ice-cold 1N aqueous HCl (400 ml). The layers were separated. The organic layer was washed with water (300 ml) and brine (300 ml), dried (Na₂SO₄), filtered and evaporated in vacuo to provide the bis-mesylate as a light yellow oil (56.0 g, 99%). ¹H NMR spectrum was satisfactory.

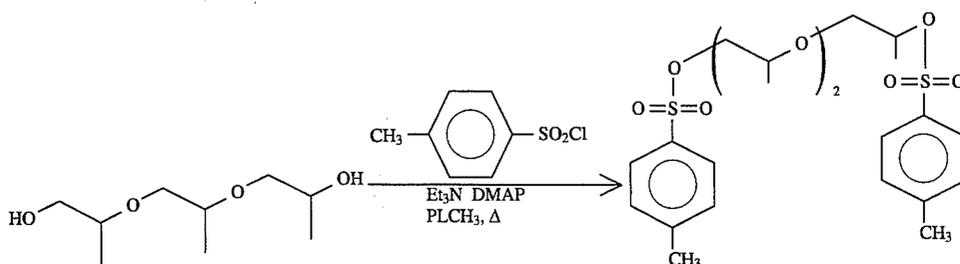
B. Preparation of Bis-(4-iodophenyl) ether of polyethylene glycol-400

The bis-mesylate of PEG-400 (15.3 g, 27.5 mmol) in dry DMF (110 ml) was reacted with 4-iodophenol (12.1 g, 55.0 mmol) and potassium carbonate (7.6 g, 55.0 mmol) at 77° C. under an atmosphere of N₂. After stirring for 16 hrs, the reaction was allowed to cool, diluted with DMF, filtered through a pad of celite and evaporated in vacuo. The resulting residue was taken up with EtOAc (500 ml), washed with 1M aqueous sodium hydroxide (200 ml), water (200 ml) and brine (200 ml), dried (Na₂SO₄), filtered, and evaporated in vacuo to provide a light brown syrup. Flash column chromatography (silica, 1%-5%; CH₃OH in CH₂Cl₂) provided bis-(4-iodophenyl) ether of polyethylene glycol-400 which was slightly contaminated with unreacted mesylates. The product was further purified by dissolving 10.5 g in DMF (100 ml). Sodium methoxide (400 mg) was added. The reaction flask was immersed in an oil bath and warmed to 93° C. After stirring for 16 hrs, the reaction was allowed to cool, diluted with EtOAc (500 ml), washed with water (200 ml) and brine (200 ml) repeatedly (3 times), dried (Na₂SO₄), filtered and evaporated in vacuo to provide a light yellow syrup. Flash column chromatography (silica, 5% CH₃OH in CH₂Cl₂) provided bis-(4-iodophenyl) ether of polyethylene glycol-400 as a light yellow syrup (8.3 g). ¹H NMR (300 MHz) analysis of the product indicates that the average number of ethylene oxide units is eight (n=8).

Title Compound: ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were consistent with the desired product.

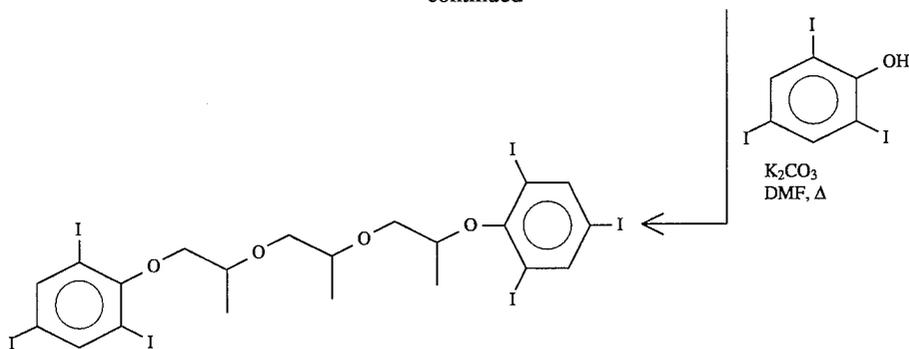
EXAMPLE 2

1,8-Bis-O-(2,4,6-triiodophenyl)-tripropylene glycol



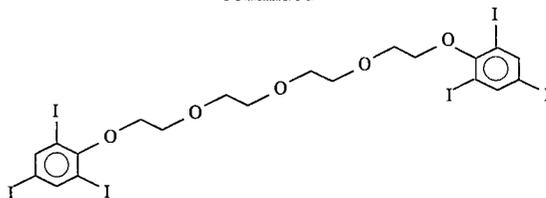
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A. Preparation of tripropylene glycol-di-p-tosylate

To a solution of tripropylene glycol (19.3 g, 100 mmol) in anhydrous toluene (400 ml) was added p-toluenesulfonyl chloride (76.5 g, 401 mmol), triethylamine (62.7 ml, 450 mmol) and dimethylamino pyridine (1.22 g, 10 mmol). The reaction was immersed in an oil bath which was warmed to 66° C. over 0.5 hr. After stirring under N₂ for 20 hrs, the reaction was allowed to cool diluted with toluene (500 ml), filtered through a pad of celite and evaporated in vacuo. The resulting residue was dissolved in CH₂Cl₂ (1 liter), washed with 5% aqueous sodium bicarbonate (500 ml), water (500 ml) and brine (500 ml), dried (Na₂SO₄), filtered and evaporated in vacuo. Flash column chromatography (silica, CH₂Cl₂) afforded tripropylene glycol di-p-tosylate (9.6 g, 19.2%) as a viscous yellow oil.

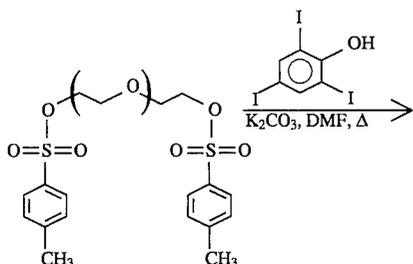
B. Preparation of 1,8-bis-O-(2,4,6-triiodophenyl)-tripropylene glycol

To a stirred solution of tripropylene glycol di-p-tosylate (9.5 g, 18.9 mmol) in dry DMF (76 ml) was added triiodophenol (18.8 g, 39.8 mmol) and potassium carbonate (5.48 g, 39.7 mmol). The reaction was immersed in an oil bath which was heated to 76° C. The reaction was stirred at 76° C for 41 hrs. At the end of this period the reaction was diluted with DMF (200 ml), filtered through a pad of celite and evaporated in vacuo. The resulting residue was dissolved in ether (300 ml), washed with 1M aqueous sodium hydroxide (100 ml), water (2×100 ml) and brine, dried (Na₂SO₄), filtered and evaporated in vacuo. Flash column chromatography (silica, 1: 1, CH₂Cl₂; hexanes) provided 1,8-bis-O-(2,4,6-triiodophenyl)-tripropylene glycol (14.8 g, 13.4 mmol) as a light yellow glass.

Title Compound: ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were consistent with the desired product. Calculated for C₂₁H₂₂O₄I₆: C, 22.93; H, 2.02; I, 69.23. Found: C, 23.23, H, 2.00; I, 69.55.

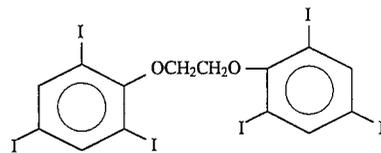
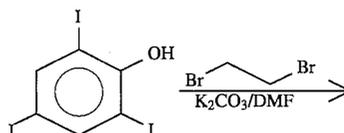
EXAMPLE 3

1,11-Bis-(2,4,6-triiodophenoxy)-3,6,9-trioxaundecane



EXAMPLE 4

1,2-Bis-(2,4,6-Triiodophenoxy)-ethane.



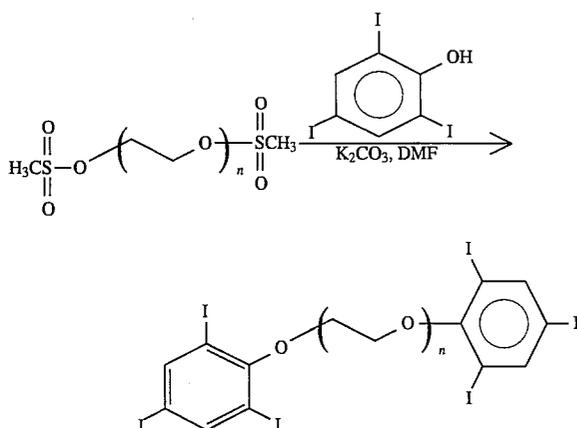
Using the procedure described for the preparation of 1,12-bis-(2,4,6-triiodophenoxy)-dodecane, 1,2-bis-(2,4,6-triiodophenoxy)ethane was prepared in 32% yield from triiodophenol (1.87 g, 3.96 mmol), milled potassium car-

9

bonate (0.66 g, 4.78 mmol, 1.2 eq) and dibromoethane (0.18 ml, 1.98 mmol) in DMF (12 ml) at 60° C. for 12 hours. Recrystallization from DMF gave white needles (1.2 g, 32%), Mp. 288°–289° C. after drying under high vacuum/110° C. Title Compound: ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were consistent with the desired product. Calculated for C₁₄H₈I₆O₂: C, 17.34; H, 0.83; I, 78.53; Found: C, 17.60, H, 0.82; I, 78.30.

EXAMPLE 5

Bis-O-(2,4,6-triodophenyl) ether of polyethylene glycol 400

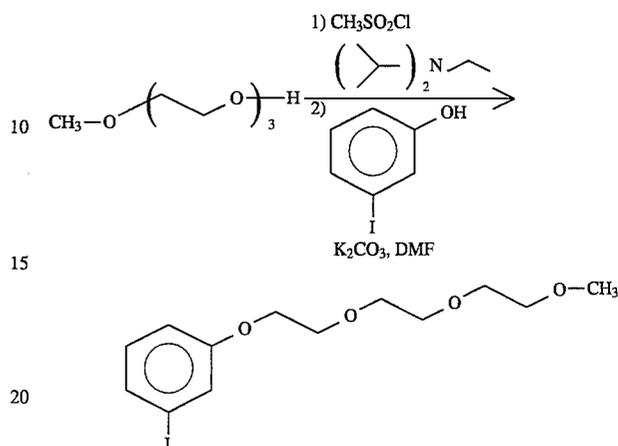


The bis-mesylate of polyethylene glycol-400 (18.7 g, 33.6 mmol) was reacted with triiodophenol (36.5 g, 77.4 mmol) and potassium carbonate (10.7 g, 77.5 mmol) in dry DMF (13.6 ml) as per bis-O-(2,4,6-triodophenyl) ether of polyethylene glycol 400 except at a temperature of 76° C. for 14 hrs followed by heating at 92° C. for 4 hrs. At the end of this period, the reaction was allowed to cool, diluted with DMF, filtered through celite and evaporated in vacuo. The residue was taken up in EtOAc (600 ml), washed with water (250 ml), 1N aqueous sodium hydroxide (250 ml), water (2×250 ml) and brine (250 ml), dried (Na₂SO₄), filtered and evaporated in vacuo to give a dark brown syrup. Flash column chromatography (silica, 1:39–1:19, CH₃OH: CH₂Cl₂) provided a brown syrup. This product was further purified by dissolution in EtOAc (500 ml), washing with saturated aqueous sodium thiosulfate (2×200 ml) and brine (200 ml), drying (Na₂SO₄) and filtering. The filtrate was treated with decolorizing carbon (10 g), heated to boiling (0.25 h), filtered and evaporated in vacuo to provide bis-O-(2,4,6-triodophenyl) ether of polyethylene glycol-400 (29 g). ¹H NMR analysis (300 MHz) of the product indicates that the average number of the ethylene oxide units is eight (n=8). Title Compound: ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were consistent with the desired product.

10

EXAMPLE 6

1-(3-Iodophenoxy)-3,6,9-trioxadecane



A, Preparation of the mesylate of triethylene glycol monomethyl ether

The mesylate was prepared via standard protocol from triethylene glycol monomethyl ether (8.2 g, 50.0 mmol), methanesulfonyl chloride (4.6 ml, 59.4 mmol) and diisopropylethylamine (11.3 ml, 64.9 mmol) in dichloromethane (100 ml) in 99% yield.

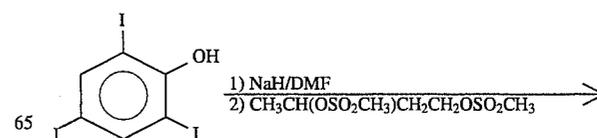
B. Preparation of 1-(3-Iodophenoxy)-3,6,9-trioxadecane

To a solution of 1-[(methanesulfonyl)-oxy]-3,6,9-trioxadecane (11.6 g, 47.9 mmol) in dry DMF (145 ml) was added 3-iodophenol (10.6 g, 48.2 mmol) and potassium carbonate (6.6 g, 47.8 mmol). The reaction was immersed in an oil bath which was warmed to 68° C. over a period of 0.5 hr. The reaction was stirred at this temperature under an N₂ atmosphere for 16 hrs and then at 82° C. for an additional 2 hrs. At the end of this period, the reaction was cooled, diluted with DMF, filtered through a pad of celite and evaporated in vacuo. The resulting residue was taken up into ethyl acetate (500 ml), washed with water (200 ml), 1N aqueous sodium hydroxide (200 ml) and brine (200 ml), dried (Na₂SO₄), filtered and evaporated in vacuo to provide a light brown oil. Flash column chromatography (silica, 1:3 to 1:2; EtOAc:hexane) provided 1-(3-iodophenoxy)-3,6,9-trioxadecane as a light yellow oil (10.8 g, 37.1%).

Title Compound: ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were consistent with the desired product. Calculated for C₁₃H₁₀O₄I: C, 42.52; H, 5.49; I, 34.56. Found: C, 42.50, H, 5.13; I, 34.78.

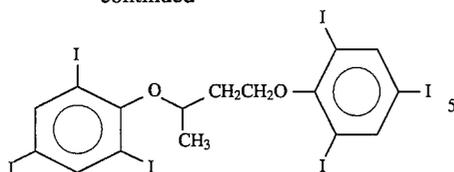
EXAMPLE 7

1,3-Bis-(2,4,6-Triiodophenoxy)-butane



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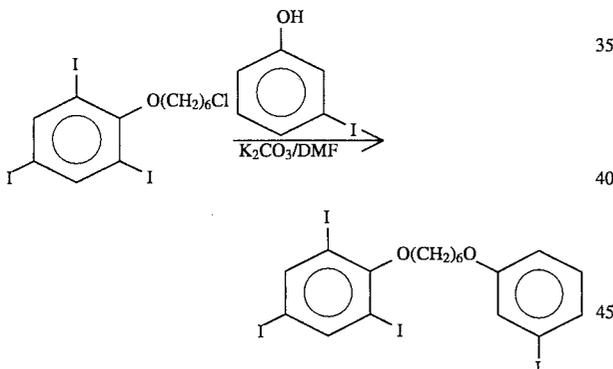


A mixture of triiodophenol (5.78 g, 12.3 mmol) and sodium hydride (0.49 g, 60% dispersion, 12.3 mmol) in DMF (15 ml) was stirred at room temperature for 1 hour and then a solution of 1,3-bis-(methanesulfonyloxy) butane (1.37 g, 5.58 mmol) in DMF (5 ml) was added. The mixture was heated to 90° C. for 6 hours and then poured into water after cooling. Ethyl acetate was added and the mixture was allowed to stand overnight. The precipitated solid was collected and dried to give 3.0 g (54%) of the desired product, Mp 173°–175° C.

Title Compound: ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were consistent with the desired product. Calculated for C₁₆H₁₂I₆O₂: C, 18.26; H, 1.21; I, 76.32; Found: C, 19.35, H, 1.16; I, 76.27.

EXAMPLE 8

1-(3-Iodophenoxy)-6-(2,4,6-triiodophenoxy)-hexane



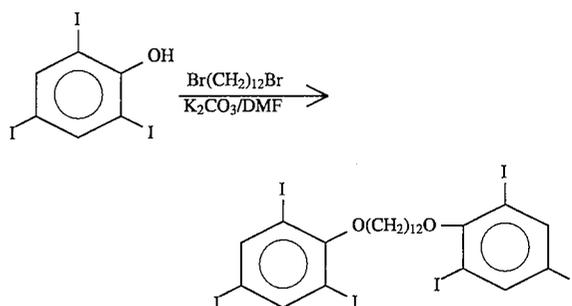
A mixture of potassium carbonate (3.0 g, 21.9 mmol, 1.1 eq), 3-iodophenol (4.4 g, 19.9 mmol) and 6-(2,4,6-triiodophenoxy)-1-chlorohexane (11.75 g, 19.9 mmol) in 50 ml of DMF was heated to 110° C. for 1.5 hours and then cooled. The mixture was poured into water and extracted with ethyl acetate. The organic layer was dried (magnesium sulfate) and evaporated to give a solid which was filtered through basic alumina (hexanes-ethyl acetate). The filtrate was concentrated under vacuum leaving the crude product as a solid. Recrystallization from cyclohexane afforded 8.29 g (54%) of the desired product after drying at room temperature under high vacuum, mp 65°–66° C.

Title Compound: ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were consistent with the desired product. Calculated for C₁₈H₁₈I₄O₂: C, 27.93; H, 2.34; I, 65.59; Found: C, 27.85, H, 2.16; I, 65.53.

12

EXAMPLE 9

1,12-Bis-(2,4,6-Triiodophenoxy)-dodecane



A mixture of triiodophenol (14.4 g, 30.5 mmol), potassium carbonate (4.6 g, 33.6 mmol, 1.1 eq) and 1,12-dibromododecane (5.0 g, 15.2 mmol) in dimethylformamide (30 ml) was heated at 120° C. for 2 hours and then cooled. The reaction mixture was poured into water (400 ml) and ethyl acetate (400 ml) was added. The solid that precipitated was collected, slurried in boiling methanol and then boiling water. The residual solid was recrystallized from dimethylformamide to give the product as a white solid (11.1 g, 66%), mp. 120°–121° C. after drying under high vacuum (0.2 torr) at 90° C.

Title Compound: ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were consistent with the desired product. Calculated for C₂₄H₂₈I₆O₂: ¼ ((CH₃)₂NCHO): C, 26.35; H, 2.66; I, 67.49; Found: C, 26.64, H, 2.47; I, 67.38.

The natural, pharmaceutically acceptable clays incorporated in the present invention comprise aluminum silicates. They are used in purified form, suitable for administration to patients. The natural, pharmaceutically acceptable clays of the present invention, generally referred to as smectites, consist of dioctahedral smectites and trioctahedral smectites.

Dioctahedral smectites include:

montmorillonite, having the formula
M⁺ Al_{3-y}(FeMg)_ySi₄O₁₀(OH)₂.nH₂O;beidellite, having the formula
M⁺ (Al₂(Si_{4-x}Al_x)O₁₀(OH)₂.nH₂O;nontronite, having the formula
M⁺(Fe₂³⁺(Si_{4-x}Al_x)O₁₀(OH)₂.nH₂O;wherein M⁺ is Na, Ca or Mg.

Trioctahedral smectites include:

saponite, having the formula
M⁺(Mg_{3-y}(AlFe)_ySi_{4-x}Al_x)O₁₀(OH)₂.nH₂O; andhectorite, having the formula
M⁺(Mg_{3-y}Li_y)Si₄O₁₀(OH)₂.nH₂O;wherein M⁺ is Na, Ca or Mg.

The clays are available from chemical suppliers, such as, for example, American Colloid Company, Arlington Heights, IL, under the tradenames:

MAGNABRITE®HS;
HECTABRITE®DP,
HECTABRITE®LT,
CARMARGO®White,
POLARGEL®NF,
POLARGEL®HV, and
VOLCLAY®NF-BC.

Other suppliers include: Engelhard Corp., Iselin, N.J.; Ashland Chemical Inc., Columbus, Ohio; RT Vanderbilt Co.,

13

Inc., Norwalk, Conn. and Whittaker Clark & Daniels, Inc., S. Plainfield, N.J.

The contrast agent and the pharmaceutically acceptable clay are formulated for administration using physiologically acceptable carriers or excipients in a manner within the skill of the art. The contrast agent with the addition of pharmaceutically acceptable aids (such as surfactants and emulsifiers) and excipients may be suspended or emulsified in an aqueous medium resulting in a suspension or emulsion.

Compositions

Compositions of the present invention comprise the following pharmaceutically acceptable components based on % w/v:

Ingredients	Broad Range	Perferred Range	Most Preferred Range
Contrast agent	5-45	10-35	15-25
Clay	0.1-10	0.5-5	1-2
Surfactant	1-20	2-10	3-5
Excipients	0-15	0.5-5	1-2
Water - q.s. to 100% by volume			

Excipients contemplated by the present invention include antifoaming agents, such as simethicone, siloxyalkylene polymers and polyoxyalkylated natural oils; preservatives, such as methyl paraben, propyl paraben, benzoic acid and sorbic acid; flavoring/sweetening agents, such as sodium saccharine; and coloring agents, such as lakes and dyes.

While the iodophenoxy alkylene ethers of the present invention in formulations with a pharmaceutically acceptable vehicle provide good quality x-ray images, the addition of a pharmaceutically acceptable clay to the formulations greatly increases the quality of the x-ray images. At the low extreme of the concentration range there is little or no benefit gained, while above the higher extreme of the concentration range the emulsion is too viscous for administration.

The following formulation examples will further illustrate the invention.

EXAMPLE 10

Components	Amounts in % w/v
Bis-(4-iodophenyl)ether of polyethylene glycol-400	17.50
HECTABRITE @DP	1.35
Polysorbate 80 (Tween 80)	1.50
Sorbitan Mono-oleate (Span 80)	1.65
q.s. with water to 100% by volume	

EXAMPLE 11

Components	Amounts in % w/v
1,8-Bis-O-(2,4,6-triiodophenyl)-tripropylene glycol	25.00
POLARGEL @NF	2.30
Polysorbate 60 (Tween 60)	1.00
Poloxamer 338	6.50
Benzoic Acid	0.50
Sorbic Acid	0.05
q.s. with water to 100% by volume	

14

EXAMPLE 12

Components	Amounts in % w/v
5 1,11-Bis-(2,4,6-triiodophenoxy)-3,6,9-trioxaundecane	17.50
MAGNABRITE @HS	1.25
Polysorbate 20 (Tween 20)	1.50
Sorbitan Mono-laurate (Span 20)	2.00
Polyvinyl Alcohol	4.00
10 Sodium Saccharin	0.30
q.s. with water to 100% by volume	

The surface active agents used in the present invention may be cationic, anionic, nonionic or zwitterionic.

15 Suitable cationic surfactants include cetyl trimethyl ammonium bromide, cetyl pyridinium chloride, myristyl gamma picolinium chloride and benzalkonium chloride. Suitable anionic agents include sodium lauryl sulphate, sodium heptadecyl sulphate, alkyl benzenesulphonic acids and salts thereof, sodium butylnaphthalene sulfonate, and sulphosuccinates. Zwitterionic surface active agents are substances that when dissolved in water they behave as diprotic acids and, as they ionize, they behave both as a weak base and a weak acid. Since the two charges on the molecule balance each other out they act as neutral molecules. The pH at which the zwitterion concentration is maximum is known as the isoelectric point. Compounds, such as certain amino acids having an isoelectric point at the desired pH of the formulations of the present invention are useful in practicing the present invention.

30 In preparing the formulations of the present invention we prefer to use nonionic emulsifiers or surface active agents which, similarly to the nonionic contrast agents, possess a superior toxicological profile to that of anionic, cationic or zwitterionic agents. In the nonionic emulsifying agents the proportions of hydrophilic and hydrophobic groups are about evenly balanced. They differ from anionic and cationic surfactants by the absence of charge on the molecule and, for that reason, are generally less irritating than the cationic or anionic surfactants. Nonionic surfactants include carboxylic esters, carboxylic amides, ethoxylated alkylphenols, ethoxylated aliphatic alcohols, ethylene oxide polymer or ethylene oxide/propylene oxide co-polymers polyvinylpyrrolidone and polyvinylalcohol.

45 One particular type of carboxylic ester nonionic surface active agents are the partial, for example mono-, esters formed by the reaction of fatty and resin acids, for example of about 8 to about 18 carbon atoms, with polyalcohols, for example glycerol, glycols such as mono-, di-, tetra- and hexaethylene glycol, sorbitan, and the like; and similar compounds formed by the direct addition of varying molar ratios of ethylene oxide to the hydroxy group of fatty acids.

50 Another type of carboxylic esters are the condensation products of fatty and resin partial acids, for example mono-, esters ethylene oxide, such as fatty or resin acid esters of polyoxyethylene sorbitan and sorbitol, for example polyoxyethylene sorbitan, mono-tall oil esters. These may contain, for example, from about 3 to about 80 oxyethylene units per molecule and fatty or resin acid groups of from about 8 to about 18 carbon atoms. Examples of naturally occurring fatty acid mixtures which may be used are those from coconut oil and tallow while examples of single fatty acids are dodecanoic acid and oleic acid.

65 Carboxylic amide nonionic surface active agents are the ammonia, monoethylamine and diethylamine amides of fatty acids having an acyl chain of from about 8 to about 18 carbon atoms.

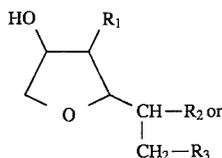
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The ethoxylated alkylphenol nonionic surface active agents include various polyethylene oxide condensates of alkylphenols, especially the condensation products of mono-alkylphenols or dialkylphenols wherein the alkyl group contains about 6 to about 12 carbon atoms in either branched chain or particularly straight chain configuration, for example, octyl cresol, octyl phenol or nonyl phenol, with ethylene oxide, said ethylene oxide being present in amounts equal to from about 5 to about 25 moles of ethylene oxide per mole of alkylphenol.

Ethoxylated aliphatic alcohol nonionic surface active agents include the condensation products of aliphatic alcohols having from about 8 to 18 carbon atoms in either straight chain or branched chain configuration, for example oleyl or cetyl alcohol, with ethylene oxide, said ethylene oxide being present in equal amounts from about 30 to about 60 moles of ethylene oxide per mole of alcohol.

Preferred nonionic surface active agents include:

30 (a) Sorbitan esters (sold under the trade name Span) having the formula:



wherein

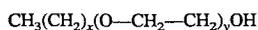
$R_1=R_2=OH$, $R_3=R$ for sorbitan monoesters,

$R_1=OH$, $R_2=R_3=R$ for sorbitan diesters,

$R_1=R_2=R_3=R$ for sorbitan triesters,

where $R=(C_{11}H_{23})COO$ for laurate, $(C_{17}H_{33})COO$ for oleate, $(C_{15}H_{31})COO$ for palmitate, $C_{17}H_{35}COO$ for stearate;

(b) Polyoxyethylene alkyl ethers (i.e. Brij's) having the formula:

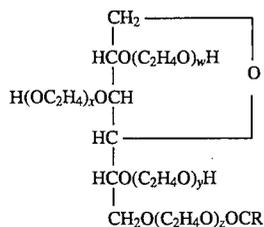


where $(x+1)$ is the number of carbon atoms in the alkyl chain, typically:

12 lauryl	(dodecyl)
14 myristyl	(tetradecyl)
16 cetyl	(hexadecyl)
18 stearyl	(octadecyl)

and y is the number of ethylene oxide groups in the hydrophilic chain, typically 10-60;

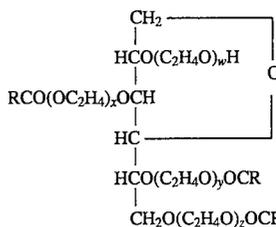
(c) Polyoxyethylene sorbitan fatty acid esters (Polysorbates 20, 40, 60, 65, 80 & 85) sold under the trade names of Tweens, Crillets, Solates and Monitans having the formulas (1) and (2)



Polyoxyethylene sorbitan monoester

16

-continued



Polyoxyethylene sorbitan triester

wherein

$W+x+y+z=20$ (Polysorbate 20, 40, 60, 65, 80 and 85)

$W+x+y+z=5$ (Polysorbate 81)

$W+x+y+z=4$ (Polysorbate 21 and 61);

(d) Polyethylene stearates, such as:

poly(oxy-1,2-ethanediyl)- α -hydro- ω -hydroxyoctadecanoate;

polyethylene glycol monostearate; and

poly(oxy-1,2-ethanediyl)- α -(1-oxooctadecyl)- ω -hydroxyoxypolyethylene glycol monostearate;

(e) Polyoxyethylene/polypropylene oxide block copolymers, sold under the name PLURONIC™, which include Poloxamer 407 (PLURONIC™ F127), Poloxamer 188 (PLURONIC™ F68), Poloxamer 237 (PLURONIC™ F87) and Poloxamer 338 (PLURONIC™ F108);

(f) Polyvinylpyrrolidone; and

(g) Polyvinylalcohol.

The dosages of the contrast agent used according to the method of the present invention will vary according to the precise nature of the contrast agent used. Preferably, however, the dosage should be kept as low as is consistent with achieving contrast enhanced imaging. By employing as small amount of contrast agent as possible, toxicity potential is minimized. For most contrast agents of the present invention dosages will be in the range of from about 0.1 to about 16.0 g iodine/kg body weight, preferably in the range of from about 0.5 to about 6.0 g iodine/kg of body weight, and most preferably, in the range of from about 1.2 to about 2.0 g iodine/kg body weight for regular x-ray visualization of the GI tract. For CT scanning the contrast agents of the present invention will be in the range of from about 1 to about 600 mg iodine/kg body weight, preferably in the range of from about 20 to about 200 mg iodine/kg body weight, and most preferably in the range of from about 40 to about 80 mg iodine/kg body weight.

When administered to mammals, the compositions of the present invention produce excellent x-ray and CT images.

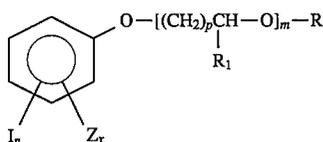
The invention, having been fully described, it will be apparent to one skilled in the art that changes and modifications can be made thereto without departing from the spirit and scope thereof.

What is claimed is:

1. An x-ray contrast composition for oral or retrograde examination of the gastrointestinal tract comprising on a % weight per volume basis:

(a) from about 5 to 45% of an x-ray contrast producing agent having the formula, or a pharmaceutically acceptable salt thereof

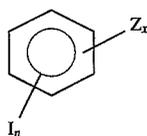
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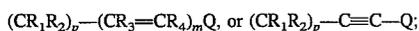
wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, alkoxy-carbonyl, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl,



or halo-lower-alkyl; each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy;



R₁, R₂, R₃ and R₄ are independently H or lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-4;

m is 1-15;

p is 1-20; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(b) from about 0.1 to 10% of a pharmaceutically acceptable clay selected from the group consisting of: montmorillonite, beidelite, nontronite, hectorite and saponite;

(c) from about 1.0 to 20% of a surfactant selected from the group consisting of nonionic, anionic, cationic and zwitterionic surfactants;

(d) from about 0 to 15% of an excipient; and

(e) water to make 100% by volume.

2. The x-ray contrast composition of claim 1 wherein said x-ray contrast producing agent is present in an amount of from about 10 to 35%.

3. The x-ray contrast composition of claim 1 wherein said pharmaceutically acceptable clay constitutes from 0.5 to 5% of the composition.

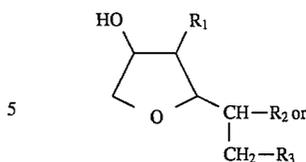
4. The x-ray contrast composition of claim 1 wherein said surfactant constitutes from 2 to 10% of the composition.

5. The x-ray contrast composition of claim 1 wherein said excipient constitutes from 0.5 to 5% of the composition.

6. The x-ray contrast composition of claim 1 wherein said nonionic surface active agent is selected from the group consisting of carboxylic esters, carboxylic amides, ethoxylated alkylphenols, ethoxylated aliphatic alcohols, ethylene oxide polymer, ethylene oxide/propylene oxide co-polymer, polyvinylpyrrolidone and polyvinylalcohol.

7. The x-ray contrast composition of claim 1 wherein said surfactant is sorbitan ester having the formula:

18



wherein

R₁=R₂=OH, R₃=R for sorbitan monoesters,

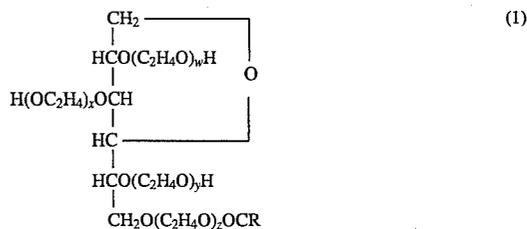
R₁=OH, R₂=R₃=R for sorbitan diesters,

R₁=R₂=R₃=R for sorbitan triesters,

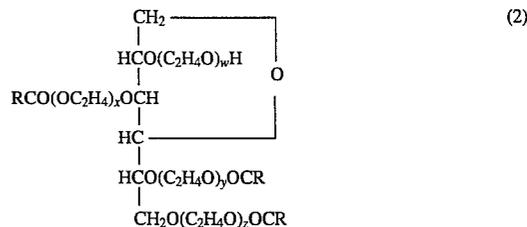
where R=(C₁₁H₂₃) COO for laurate, (C₁₇H₃₃) COO for oleate, (C₁₅H₃₁) COO for palmitate or (C₁₇H₃₅) COO for stearate.

8. The x-ray composition of claim 1 wherein said surface active agent is polyoxyethylene stearate.

9. The x-ray contrast composition of claim wherein said surfactant is polyoxyethylene sorbitan fatty acid ester of the formulas (1) and (2)



Polyoxyethylene sorbitan monoester



Polyoxyethylene sorbitan triester

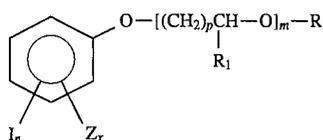
wherein w+x+y+z is selected from the group consisting of 20, 5, and 4.

10. The x-ray contrast composition of claim 1 wherein said x-ray contrast producing agent is selected from the group consisting of: bis-(4-iodophenyl) ether of polyethylene glycol-400, 1,8-bis-O-(2,4,6-triiodophenyl)-tripropylene glycol, 1,11-bis-(2,4,6-triiodophenoxy)-3,6,9-trioxaundecane, 1,2-bis-(2,4,6-triiodophenoxy)-ethane and bis-O-(2,4,6-triiodophenyl)-ether of polyethylene glycol-400.

11. The x-ray contrast composition of claim 1 wherein said x-ray contrast producing agent is selected from the group consisting of: 1-(3-iodophenoxy)-3,6,9-trioxadecane, 1,3-bis-(2,4,6-triiodophenoxy)-butane, 1-(3-iodophenoxy)-6-(2,4,6-triiodophenoxy)-hexane and 1,12-bis-(2,4,6-triiodophenoxy)-dodecane.

12. A method of carrying out x-ray examination of the gastrointestinal tract of a patient, said method comprises the oral or rectal administration to the patient an x-ray contrast formulation comprising:

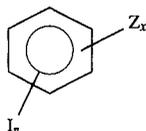
(a) from about 5 to 45% of an x-ray contrast producing agent having the formula, or a pharmaceutically acceptable salt thereof



wherein

Z is H, halo, C₁-C₂₀ alkyl, cycloalkyl, lower alkoxy, alkoxy-carbonyl, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C₁-C₂₅ alkyl, cycloalkyl,



or halo-lower-alkyl; each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy;

(CR₁R₂)_p-(CR₃=CR₄)_mQ, or (CR₁R₂)_p-C≡C-Q;

R₁, R₂, R₃ and R₄ are independently H or lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-4;

m is 1-15;

p is 1-20; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower alkyl;

(b) from about 0.1 to 10% of a pharmaceutically acceptable clay selected from the group consisting of: montmorillonite, beidelite, nontronite, hectorite and saponite;

(c) from about 1.0 to 20% of a surfactant selected from the group consisting of nonionic, anionic, cationic and zwitterionic surfactants;

(d) from about 0.0 to 15% of an excipient; and

(e) water to make 100% by volume.

13. The method of claim 12 wherein said x-ray contrast producing agent is present in an amount of from about 10 to 35%.

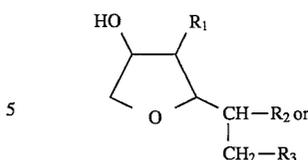
14. The method of claim 12 wherein said pharmaceutically acceptable clay constitutes from 0.5 to 5% of the composition.

15. The method of claim 12 wherein said surfactant constitutes from 2 to 10% of the composition.

16. The method of claim 12 wherein said excipient constitutes from 0.5 to 5% of the composition.

17. The method of claim 12 wherein said nonionic surface active agent is selected from the group consisting of carboxylic esters, carboxylic amides, ethoxylated alkylphenols, ethoxylated aliphatic alcohols, ethylene oxide polymer, ethylene oxide/propylene oxide co-polymer, polyvinylpyrrolidone and polyvinylalcohol.

18. The method of claim 12 wherein said surfactant is sorbitan ester having the formula:



wherein

R₁=R₂=OH, R₃=R for sorbitan monoesters,

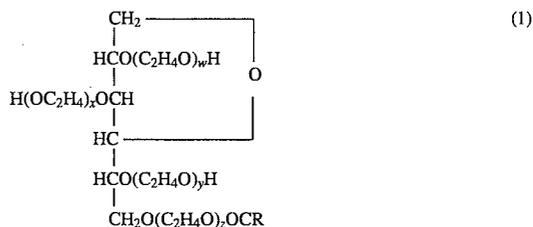
R₁=OH, R₂=R₃=R for sorbitan diesters,

R₁=R₂=R₃=R for sorbitan triesters,

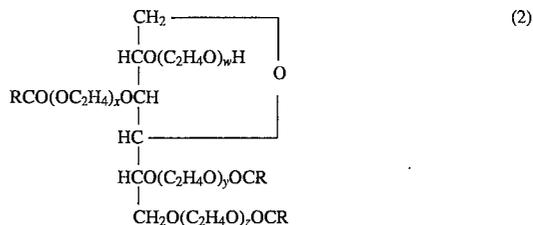
where R=(C₁₁H₂₃) COO for laurate, (C₁₇H₃₃) COO for oleate, (C₁₅H₃₁) COO for palmitate or (C₁₇H₃₅) COO for stearate.

19. The method of claim 12 wherein said surface active agent is polyoxyethylene stearate.

20. The method of claim 12 wherein said surfactant is polyoxyethylene sorbitan fatty acid ester of the formulas (1) and (2)



Polyoxyethylene sorbitan monoester



Polyoxyethylene sorbitan triester

wherein w+x+y+z is selected from the group consisting of 20, 5, and 4.

21. The method of claim 11 wherein said x-ray producing agent is selected from the group consisting of: bis-(4-iodophenyl) ether of polyethylene glycol-400, 1,8-bis-O-(2,4,6-triiodophenyl)-tripropylene glycol, 1,11-bis-(2,4,6-triiodophenoxy)-3,6,9-trioxaundecane, 1,2-bis(2,4,6-triiodophenoxy)-ethane and bis-O-(2,4,6-triiodophenyl)-ether of polyethylene glycol-400.

22. The method of claim 11 wherein said x-ray producing agent is selected from the group consisting of 1-(3-iodophenoxy)-3,6,9-trioxadecane, 1,3-bis-(2,4,6-triiodophenoxy)-butane, 1-(3-iodophenoxy)-6-(2,4,6-triiodophenoxy)-hexane and 1,12-bis-(2,4,6-triiodophenoxy)dodecane.

* * * * *